An Introduction to the Center for Biologics Evaluation and Research

"CBER 101"

CLINICAL TRIAL DESIGN

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CBER/FDA

Clinical Trial Design

- Code of Federal Regulations
- ICH E6 (Good Clinical Practice)
- ICH E8 (General Considerations for Clinical trials)

Appropriate Trial Design

- Answer relevant scientific question
- Protection of trial subjects
- Part of an overall development plan
- Objectives appropriate for the Phase of Development

Appropriate Trial Design

- Goal of successful product development:
  - Lead to licensing of new products or new indications for marketed products
    - 21 CFR 601: product must meet safety, purity and **potency**
    - CBER interprets potency as effectiveness shown in adequate and well-controlled studies (F D & C Act, 1962 and 21 CFR 314.126).

Appropriate Trial Design

- Think international !
  - International Conference on Harmonisation
  - Multinational studies in rare diseases or when large sample sizes are required
  - Uniform format for US, Japan and EU regulatory review

Phases of Development

- Phase I
  - "Pilot" study
  - Supported by non clinical pharmacokinetic and toxicity data
  - Objective:
    - Emphasis on safety and frequent AE's
    - Study pharmacology (PK, PD)
  - Small sample size
    - Some studies can include healthy volunteers (risks vs. benefits)

Phases of Development

- Phase II
  - "Exploratory" study
  - Dose ranging, schedule and route of administration studies in the target population
  - More strict eligibility criteria acceptable (sometimes preferable)
  - Design supported by data from Phase I and pre-clinical information

Phases of Development

- Phase III
  - Study Design based on Phase 2
  - End of Phase 2 meeting with FDA
  - “Confirmatory” Study
  - Fewer doses or dosing regimens
  - Controlled study or studies

Phases of development

- Phase IV
  - Post approval
  - Long term safety, rare AE's
  - "Real world" experience
  - Expand product use to other sub groups of the intended population

Investigator Brochure

- Required unless single center sponsor-investigator
- Briefly describe:
  - Drug substance & formulation
  - Summary animal & human tox., PK/PD
  - Summary of safety and effectiveness in humans from prior studies
  - Anticipated risks and side effects, special precautions and monitoring
- Update as new information available

Components of a Protocol

- Rationale
- Hypothesis
- Background information
- Design
- Treatment Groups / Regimen
- Eligibility
- Patient Monitoring and Procedures
- Endpoints and Statistical Plan

Issues in Study Design

- Study Blind
  - Open label, single-blind, double-blind
- Treatment groups
- Choice of control group (ICH E10)
  - Parallel, sequential, crossover
- Randomization
  - Fixed, simple, block, stratified, adaptive, none

Safety Assessment

- Safety monitoring essential in all phases
- Safety:
  - Active collection of adverse events
  - Clinical laboratory, imaging, ancillary
  - Immunogenicity
  - Stopping rules
    - e.g.: Common Toxicity Criteria NCI
  - Independent DSMB

Safety Reporting

- Expedited Safety reporting:
  - Written ("IND Safety Report") < 15 days
    - Any **serious and unexpected** AE
    - Any pre-clinical findings suggestive of significant risks to human subjects (includes mutagen., teratogen., carcinogenicity)
  - Phone/fax reports < 7 days:
    - Fatal or life-threatening event associated with the product
- Summary of safety in Annual reports

Study Endpoints

- Well and prospectively defined
- Best to demonstrate efficacy
- Best to demonstrate clinical relevance
- Time to event vs. ascertainment rates of success at specific time points
- Feasibility

Statistical Analyses

- Group to include (ITT preferable)
- Appropriate for endpoints selected
- Primary vs. exploratory analysis
- Prospective vs. post-hoc analysis
- P value (two tailed) and CI
- How to deal with missing data and protocol deviations
- Sub group analyses

Study Monitoring

- Adequate mechanisms to monitor and audit study conduct to achieve interpretable data.
- Performed by the sponsor or designated qualified monitors (e.g. CRO)
- “No study is better than the quality of its data”*

*Fundamentals of Clinical Trials, Friedman, et al.

Code of Federal Regulations

- 21 CFR
  - 50 - Protection of Human Subjects
  - 56 - Institutional Review Boards
  - 312 - INDs
  - 601 - Biologics Licensing

  - (314 – Rare NDA's in CBER, but interpretation of evidence of efficacy)